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EDITORIAL COMMENT

Go Set a Watchman?*

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"Every man's island…every man's watchman, is his conscience."
—Harper Lee, Go Set a Watchman: A Novel (1)

"For thus hath the Lord said unto me, Go, set a watchman, let him declare what he seeth."
—Book of Isaiah 21:6 (2)

The recent approval of the WATCHMAN device (Boston Scientific, Natick, Massachusetts) by the U.S. Food and Drug Administration (FDA) is a milestone for the subspecialty of structural cardiology. The WATCHMAN device is indicated for patients with nonvalvular atrial fibrillation (NVAF) who are at increased risk of stroke and are suitable for anticoagulation with warfarin, but for whom there is a reasonable rationale to undergo nonpharmacological alternative therapy (3).

Closing the left atrial appendage (LAA) in patients with NVAF to prevent stroke makes mechanistic sense. In a classic surgical series of patients with NVAF, 91% of left atrial thrombi were found to be anchored in or confined to the LAA (4). Indirect evidence suggests that warfarin eliminates thrombi from the LAA (5), and strong evidence shows that adjusted-dose warfarin reduces stroke by about 60% in NVAF (6), thus defining 1 of the most successful treatments in cardiovascular medicine.

Because warfarin causes bleeding and needs constant monitoring, the search for nonpharmacological approaches to exclude the LAA has been intense. Investigation of the WATCHMAN device began in the PROTECT AF (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial (7), which met its noninferiority hypothesis but showed higher rates of the safety outcomes of major bleeding, pericardial effusion, and device embolization with WATCHMAN than with chronic warfarin (relative risk [RR]: 1.69; Bayesian credible interval: 1.01 to 3.19). To address the safety issue, further investigation was undertaken in the PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial (8), which failed to demonstrate noninferiority of the WATCHMAN device compared with warfarin for the initial coprimary endpoint, but succeeded in satisfying the primary safety goal. The FDA's Circulatory System Devices Panel reviewed the WATCHMAN data on 3 occasions and ultimately recommended approval on October 14, 2014, on the basis of a split vote of 6 to 5 that favored the benefits of WATCHMAN over its risks for reducing thromboembolism in high-risk patients with NVAF (9).

A subsequent meta-analysis (10) showed that use of the WATCHMAN device caused fewer hemorrhagic strokes (0.15 events vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; $p = 0.004$) but more ischemic strokes (1.6 events vs. 0.9 events/100 PY; HR: 1.95; $p = 0.005$) than did chronic warfarin therapy. Exploratory analyses found that the use of the WATCHMAN was associated with fewer cardiovascular deaths (1.1 events vs. 2.3 events/100 PY; HR: 0.48; 95% confidence interval [CI]: 0.28 to 0.81; $p = 0.006$) but not with lower all-cause mortality (HR: 0.73; 95% CI: 0.52 to 1.00; $p = 0.07$). Post-hoc analyses that excluded periprocedural complications found that the use of the WATCHMAN was associated with fewer hemorrhagic events between 7 days and 2.7 years after randomization than was long-term warfarin (0.2 events vs. 1.0 events/100 PY; HR: 0.22; $p = 0.004$).

In this issue of *JACC: Cardiovascular Interventions*, Price et al. (11) present more details about bleeding with the WATCHMAN device from a pooled, patient-level analysis of the PROTECT AF (7) and PREVAIL

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(8) trials. The investigators found that the overall rate of major bleeding was no different after WATCHMAN implantation or long-term warfarin during 3.1 years of follow-up (3.5 events vs. 3.6 events/100 PY; RR: 0.96; 95% CI: 0.66 to 1.39; p = 0.97). Post-hoc analyses excluding periprocedural events found that LAA closure was associated with reduced bleeding

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between 7 days and 3.1 years of follow-up (1.8 events vs. 3.6 events/100 PY; RR: 0.49; 95% CI: 0.32 to 0.75; p = 0.002). Subgroup analyses that excluded periprocedural events and identified patients who were able to stop all anticoagulant and antiplatelet therapy found again that LAA closure was associated with reduced bleeding between 6 months and 3.1 years after randomization compared with long-term warfarin (1.0 events vs. 3.5 events/100 PY; RR: 0.28; 95% CI: 0.16 to 0.49; p < 0.001).

The primary bleeding outcomes in the current report (11) are disconcerting, given that the rationale for using WATCHMAN implantation in place of long-term warfarin is to reduce bleeding, and the post-hoc subgroup comparisons that eliminate periprocedural bleeding from the comparisons should be viewed as biased to favor use of the WATCHMAN device. Despite concerns about the secondary analyses, the WATCHMAN investigational program (7,8,10,11) nevertheless constitutes the best evidence for a nonpharmacological alternative to long-term warfarin to prevent stroke in NVAF. No other device for LAA closure has been studied as rigorously. The Amplatzer Cardiac Plug (St. Jude Medical, St. Paul, Minnesota) has been used outside of the United States under the CE (Conformité Européenne) mark, despite little evidence to support its use (3). The Lariat (SentreHeart, Redwood City, California), which is also CE marked and has received FDA approval as a method of soft tissue approximation but not stroke prevention, is being used off-label in clinical practice for LAA occlusion (3). Recent reports of deaths and adverse events on the FDA's Mechanical and User Facility Device Experience Database (12) suggest that there should be a moratorium on the use of Lariat or restriction to a compassionate-use basis until evidence of safety is produced.

Lest some readers view this editorial comment as a feuilleton—a first-person filleting of a topic—I will dispel that notion and conclude that the WATCHMAN device has successfully undergone scientific and regulatory scrutiny, fills an important clinical need, and despite concerns about how bleeding was analyzed in well-executed clinical trials, should be considered on a selective basis for high-risk patients with NVAF who cannot tolerate long-term warfarin therapy. Before LAA closure becomes a regular consideration for patients with NVAF who wish to avoid taking warfarin, more observation is required in a literal, biblical, and rigorously scientific sense to determine whether WATCHMAN implantation compared with long-term warfarin actually lowers the risk of bleeding in patients with NVAF.

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